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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,936	11/30/2001	Sathyamangalam V. Balasubramanian	19226/2071 (R-5659)	5734

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Michael L. Goldman
NIXON PEABODY LLP
Clinton Square
P.O. Box 31051
Rochester, NY 14603

EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,936	BALASUBRAMANIAN ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,7,8,9*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT TO IDS AND STAUS OF THE CLAIMS

1. The information disclosure statement (IDS) and Form PTO-1449 filed 4/25/02, 6/25/02, 9/9/02, 11/15/02 and 2/19/03 are acknowledged, entered and considered. Claims 1-26 are present for examination.

CLAIMS REJECTION-35 U.S.C. § 112^{2nd} PARAGRAPH

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 12, 15 and 20-22 are indefinite in the recitation the acronym "AHF". Use of full terminology at least in the first occurrence would obviate this rejection.

CLAIMS REJECTION-35 U.S.C. § 103(a)

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/55306 in view of Balasubramanian et al. (Pharmaceutical Research, Vo. 17, No. 3, pp. 344-350, March 2000) and Papahadjopoulos et al. (Proc. Natl. Acad. Sci. USA, Vol. 88, pp. 11460-11464, December 1991).

The prior art of WO 99/55306 teaches the use of pharmaceutical composition comprising Factor VIII (FVIII) and neutral liposomes wherein the protein or polypeptide (FVIII) is capable of binding the colloidal particles and polyethylene glycol (PEG), and not encapsulated in the colloidal particles, rather encapsulated in the liposomes, and the organic solvent is removed from lipid mixture by lyophilization and then reconstituted in water and thus obtained liposomes are reduced in size, wherein the process includes cooling and dialysis . Hence, the reference clearly teaches the use and complexing of FVIIII which is antihemophilic (AHF) protein and liposome in a pharmaceutical formulation. (See e.g., abstract, page 3, lines 26 to page 4, lines 4; page 5, lines 9 to page 7, lines 19; and Examples 1-4) as directed to claims 1-5, 8-15 and 20.

Thus, the primary reference of WO 99/55036 teaches method and composition that is basically the same as the instantly claimed invention, except a) does not disclose the use of liposomes as a stabilizer, b) altering the conformational state of the protein, and c) binding a stabilizer to said protein. However, the reference of Balasubramanian et al. discloses the partial unfolding which resulted in increased exposure of hydrophobic domains and aggregates of KP6β (a yeast toxin used as a model protein), but with preservation of secondary structure. Liposomes interacted with the structured intermediate state, stabilizing the protein against aggregation. These results suggest a general formulation strategy of proteins, in which partially unfolded structures are stabilized by formulation excipients that act as molecular chaperons to avoid physical instability. Thus, showing that liposomes bound to partially unfolded structures and prevented the formation of aggregates, and as such, the reference teaches the use of liposomes as stabilizers for protein. Also, the reference teaches and/or suggests a formulation strategy for protein (any protein of interest) pharmaceutical that form partially folded structures; in which the first step is to form "structured" intermediate state; in this case, the intermediate states are formed by thermally unfolding the protein, although, other methods of unfolding are possible. The second stage is to add stabilizing excipients such as liposomes to bind the intermediates. Thus, clearly showing the step of altering the conformational state of the protein and the binding step of a stabilizer to said protein of interest (See e.g., pages 344 and 349) as directed to claims 6, 7, 16-19 and 21-26. Further, the reference of Papahadjopoulos et al. teachers the use of sterically stabilized liposomes as an effective carrier system for a variety of

pharmacologically active macromolecules in which resulted in better encapsulation of a variety of positively charged drugs and other macromolecules and reduced the likelihood of aggregation (See e.g., pages 11460, 1463 and 11464) as directed to claims 7, 13, 14, 16-19 and 21-26.

In view of the above, it would have been obvious to one of ordinary skill in the art to combine the secondary references because the secondary references teach the advantages of the use of liposomes as stabilizers, altering the conformational state of the protein, and binding a stabilizer to said protein for the intended purpose of employing a method for complexing AHF in dispersed medium and thereby obtaining a pharmaceutically effective stabilized AHF formulation thereof. With respect to the selection of the appropriate chemical and physical perturbant and the percentages of the protein molecules; the secondary reference of Balasubramanian et al. teaches the use of physical perturbant comprising a thermal unfolding (change) and suggests that the other methods of unfolding are possible. Although, the prior art does not disclose the specific percentages of the protein molecules as claimed. Nevertheless, the protein disclosed by the prior art and the claimed specific percentages overlap in scope, and as such, it is conventional and within the ordinary skill in the art to optimize or select the specific percentages of the protein molecules claimed from the proteins of the prior art.

Thus, in view of the above, it would have been obvious to one of ordinary skill in the art to combine the secondary references teachings into the primary reference's teachings because such features of using liposome as stabilizer and binding the stabilizer into protein of interest are known or suggested in the art as seen in secondary

references, and including such features into the methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

With respect to claim 20, the claim is in product-by-process format, and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the recited process steps, *In re Brown*, 173 USPQ 685 (CCPA 1972); *In re Wertheim*, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, *In re Best*, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to Applicants. *In re Fitzgerald*, 205 USPQ 594.

Therefore, in view of the above, and in view of the combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known method of complexing AHF protein associated with a dispersing system such as liposomes through complexing association, including encapsulation of the liposomes and methods of preparation and use thereof. Thus, claims 1-26 are *prima facie* obvious over the combined teachings of the prior art, absence of sufficient objective factual evidence or unexpected results to the contrary.

CONCLUSION AND FUTURE CORRESPONDENCE

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

AM Mohamed/AAM

December 15, 2003

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600